Available online on 15.04.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Research Article

Electrocardiographic Abnormalities in Adult Homozygous Sickle Cell Disease Patients in Nnamdi Azikiwe University Teaching Hospital, Nnewi, South-Eastern Nigeria

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Article Info:

Article History:

Received 01 Feb 2024
Reviewed 04 March 2024
Accepted 19 March 2024
Published 15 April 2024

Emegoakor CI, Ahaneku GI, Okechukwu CU, Nwaneli UC, Osuji CU, Electrocardiographic Abnormalities in Adult Homozygous Sickle Cell Disease Patients in Nnamdi Azikiwe University Teaching Hospital, Nnewi, South-Eastern Nigeria, Journal of Drug Delivery and Therapeutics. 2024; 14(4):33-41

DOI: http://dx.doi.org/10.22270/jddt.v14i4.6491

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Abstract

Background; Sickle cell anaemia is the most common monogenic hematologic disorder in Nigeria. Cardiovascular pathology, resulting in electrocardiographic abnormalities are a common finding in adult sickle cell patients.

Objective; This study investigated the pattern of electrocardiographic (ECG) abnormalities in steady state adult sickle cell anaemia (HbSS) patients and compared the findings with that of age and sex matched Haemoglobin AA(HbAA) controls.

Methodology; Fifty steady state adult HbSS participants were recruited from the haematology clinic at Nnamdi Azikiwe University Teaching Hospital while fifty age and sex matched HbAA controls were recruited from the hospital community. Participants underwent resting 12 lead ECG using a Schiller CARDIOVIT AT-1 ECG machine. Data was analyzed using Statistical Package for Social Sciences version 21.

Results; The prevalence of ECG abnormalities amongst the adult sickle cell participants and controls was 70% and 10% respectively. ECG abnormalities were more common amongst male sickle cell participants and left ventricle hypertrophy was the most frequent ECG abnormality detected.

Conclusion; There is a high prevalence of ECG abnormalities amongst adult sickle cell anaemia patients. Regular Electrocardiography is recommended for early detection of these abnormalities for early treatment and improved quality of life.

Keywords: Electrocardiographic Abnormalities, Sickle Cell Disease Patients, Nnamdi Azikiwe University, Haemoglobin AA

INTRODUCTION

Sickle cell anaemia is a hematologic disorder that results from the inheritance of the sickle(S) hemoglobin gene in the homozygous state (HbSS).[1] It is a major public health challenge in Nigeria, due to its disabling complications and high prevalence which has been reported to be 2-3.5%.[2] The burden of the disease is highest in sub-saharan Africa.[3] The condition is associated with a significant degree of morbidity and mortality, being characterized by recurrent episodes of ischemia-reperfusion injury to multiple vital organs and a chronic haemolytic anaemia, leading to progressive organ dysfunction.[4]

The cardiovascular system is adversely affected by the disease and a wide range of cardiovascular abnormalities abound in sickle cell anaemia, and these become more manifest as patients grow older.[4] Consequently, electrocardiographic abnormalities are common findings in patients with this disease. Incidentally, most studies done to describe the electrocardiographic findings in them were done in children.[5,6] Seventy two percent of adult sickle cell patients in an American study had electrocardiographic abnormalities with the common findings noted to be increased P wave dispersion, Q wave dispersion and non-specific ST-T wave changes.[7] A study done in Lagos, south-western Nigeria, showed an overall prevalence of electrocardiographic abnormalities in adult sickle cell patients to be 73.1%.[8]

It is necessary to investigate the pattern of electrocardiographic abnormalities in adult persons with sickle cell anemia. ECG being cheap and widely available may be a key screening tool to select SCA patients for further cardiovascular evaluation. The aim of the study was to determine the pattern of electrocardiographic abnormalities in steady state adult sickle cell anaemia patients attending the haematology clinic at the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi, South East Nigeria.

MATERIALS AND METHODS

The study was a cross sectional descriptive study comprising 50 consecutive adult sickle cell anaemia patients who were in steady state, attending the haematology clinic of NAUTH Nnewi, South East Nigeria as well as 50 age and sex matched HbAA controls. Steady state was defined as absence of crisis within the previous 4 weeks and absence of any symptom or

sign attributable to acute illness.[9] The controls were mostly students and staff of the hospital whose haemoglobin genotype was confirmed by electrophoresis to be HbAA. Exclusion criteria were sickle cell anaemia patients who were in crisis or weren't in steady state, those who did not give consent to participate in the study, patients on drugs that could affect the ECG such as, beta blockers, anti arrhythmics, non-dihydropyridine calcium channel blockers**,** presence of congenital heart diseases and hypertensives. Ethical approval was sought and obtained from the ethical committee of NAUTH before commencement of the study. Participants' information was collected using a questionnaire to obtain biographical information. Important medical history such as hypertension and diabetes were obtained. Information as regards drug history was also obtained.

ECG Procedure

A resting standard 12 lead ECG was performed on participants using Schiller CARDIOVIT AT-2 plus ECG machine with the participant lying supine. The ECG paper was set at a speed of 25mm/s and the standardization was set at 10mm per millivolt. The rhythm and rate were assessed from the ECG. Upright P waves in lead II, inverted P wave in lead aVR, and biphasic P waves in lead V1, followed by QRS complexes at regular intervals was termed sinus rhythm.[10,11] The heart rate was estimated by dividing 1500 with the number of small boxes between two consecutive R waves.[10,11] Right atrial enlargement was defined as a P wave amplitude of more than 2.5mm in lead II.[12] Left atrial enlargement was defined as widened P wave (>0.12s) in lead II and/or a biphasic P wave in lead V1 with a terminal negative deflection of >1mm in amplitude and >0.04s in duration.[12,13] The QRS duration, axis and morphology were obtained. Right ventricular hypertrophy was defined as dominant R wave in V1(R wave >6mm and/or R/S >1).[12,14] Assessment of left ventricular hypertrophy was based on three criteria. The first was the Sokolow and Lyon voltage criteria,(S wave in V1 + R wave in lead V5 or V6> 35mm).[12,15,16] LVH was also defined with the Cornell voltage(SV3 + RaVL >28mm in men or >20mm in women).[12,17] Finally, Araoye code system (SV2 + RV6 > 35mm in women or > 40mm in men or RI > 12mm in both sexes), was also used to check for LVH.[16] The QT interval was measured from the beginning of the QRS complex to the end of the T-wave in all the leads with discernable positive T waves and the longest QT interval was used.[18] It was corrected for heart rate with Bazett's correction formula.[19] QTc was defined as prolonged when >0. 45s in males or > 0.46s in female or abnormally short when < 0.39s in both sexes.[18] The QT dispersion was the difference between the longest and shortest QT interval.[18] QRS durations >0.12s were deemed broad. Right bundle branch block was defined by a QRS duration that is greater than or equal to 0.12s with positive late deflection in V1 and/or V2 and also with S wave duration of greater than 0.04s in leads V6 and 1.[20] Left bundle branch block was defined, when there was a broad QRS with dominant S wave in V1 with broad, notched or slurred R wave in leads 1, aVL, V6 or V5.[20] A QRS axis as from 90 degrees to 180 was termed as Right axis deviation, whereas a QRS axis from -30 degrees to -90 degrees was termed as left axis deviation. [20]

Data was analyzed using Statistical Package for Social Sciences (SPSS), software version 21. Socio-demographic characteristics of the participants were presented with simple descriptive statistics. Continuous variables were presented as mean and standard deviation and median as appropriate whereas categorical variables were presented as proportions and percentages.

Comparison of continuous variables that were normally distributed between sickle cell anaemia patients and the HbAA controls was made with independent student's t-test while continuous variables that were not normally distributed was made with Mann-Whitney U test. For categorical variables, proportions between both groups were compared with Chi-square test and Fishers exact test as appropriate (in the later case, where an expected cell is less than 5).

For tests that were significant at univariate level, logistic regression (for categorical dependent variable) and effect size (for continuous variables) was used to determine the strength of the association. Statistical tests were two tailed and p values less than 0.05 were regarded as statistically significant.

RESULTS

The socio-demographic characteristics of the study participants are shown in Table 1. Fifty participants (25 males and 25 females) with Sickle Cell Anaemia (HbSS) were recruited for this study as cases and fifty HbAA participants (25 males and 25 females) were recruited as controls. There was no statistically significant sex difference between Sickle Cell Anaemia (HbSS) participants and HbAA control subjects (p=1.00).

Table 1: Socio-demographic characteristics of the study participants **N=100**

Variables	HbSS (n=50)	HbAA (n=50)	p-value
Mean Age (years) (SD)	27.80(7.09)	28.66(6.55)	0.53
Gender			
Male	25(50.0%)	25(50.0%)	1.00
Female	25(50.0%)	25(50.0%)	
Marital Status			
Single	46(92.0%)	33(66.0%)	0.03*
Married	4(8.0%)	17(34.0%)	
Level of Education			
Primary	2(4.1%)	1(2.0%)	0.38
Secondary	16(32.7%)	11(22.0%)	
Tertiary	31(63.3%)	38(76.0%)	
Employment Status			
Employed	16(37.2%)	27(54.0%)	0.06
Unemployed	6(14.0%)	1(2.0%)	
Students	21(48.8%)	22(44.0%)	

** Statistically significant*

The mean age of the HbSS group was 27.80 years while the mean age of the HbAA group was 28.66 years. There was no statistically significant age difference among the study participants (p=0.53).

Forty-six (92%) of the HbSS group were single while only four (8%) of them were married. However amongst the control group, thirty three (66%) were single, while seventeen (34%) were married. This difference in marital status was statistically significant (p=0.03). All the study participants had at least primary school education.

Fig 1 shows the prevalence of abnormal ECGs. The prevalence of abnormal ECGs in the sickle cell group was 70%, while the prevalence amongst controls was 10%. This was statistically significant (p=<0.001).

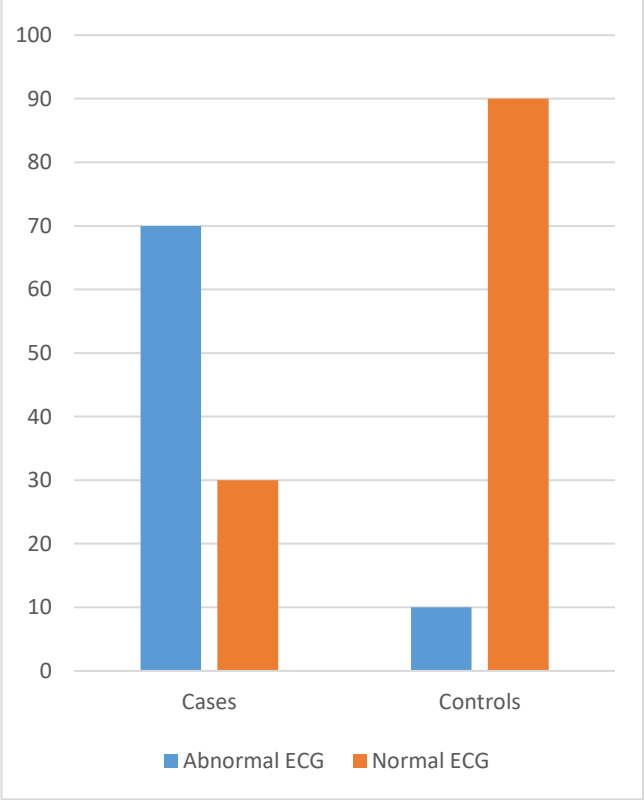

Figure 1: Prevalence of Abnormal ECGs

Fig 2 shows the sex prevalence of abnormal ECGs within the sickle cell group. 92% of male sickle cell participants had ECG abnormalities while only 8% had normal ECG. Amongst the female sickle cell participants, 48% had ECG abnormalities, while 52% had normal ECG. This difference was statistically significant (p=0.001). Male sicklers were twelve times more likely to have at least one ECG abnormality than their female counterparts.

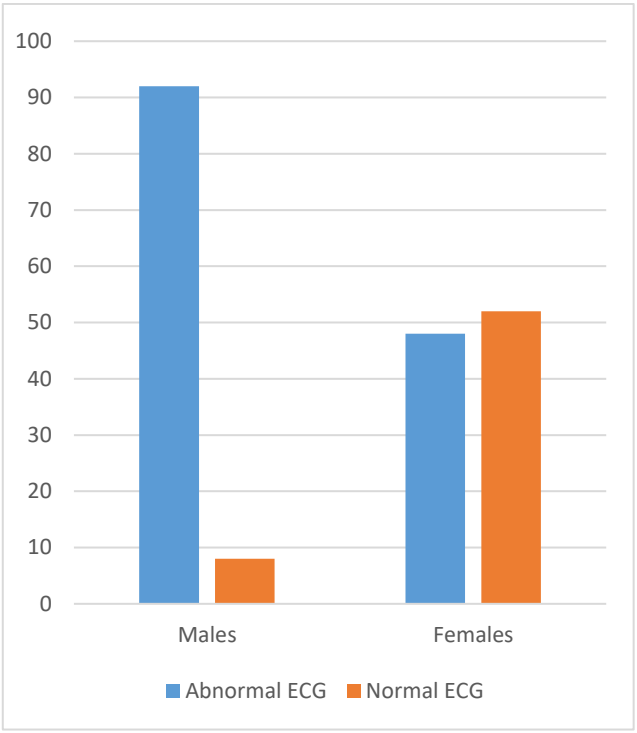

Figure 2: Sex Prevalence of Abnormal ECGs within the sickle cell group.

Comparison of the patterns of ECG findings between sicklers and Control

Table 2 shows the pattern of some electrocardiographic (ECG) findings of study participants. The sickle cell group had a stastically significant higher mean heart rate (78.38) than the control group (71.38). All but one participant in the HbSS group were in sinus rhythm whereas all the participants in the control group were in sinus rhythm. None of the participants in both groups had right atrial or left atrial enlargement. All the study participants had normal QRS axis. Amongst the male participants in the HbSS group, 20(80.0%) had a normal QTc, 3(12.0%) had short QTc, and 2(8%) had prolonged QTc. Amongst the male participants in the control group, 8(33.3%) had normal QTc, 16(66.7%) had short QTc, and none had a prolonged QTc. This difference in the QTc parameters was statistically significant (p=<0.001). Amongst the females, there was no statistical difference in the QTc parameters between both groupsvalue among the female participants was not statistically significant (p=0.11).

QT dispersion was present in 18(36.0%) participants in the sickle cell group as against 9(18.0%) participants in the control group. This was a statistically significant difference (p=0.04), with the sicklers twice more likely to have QT dispersion than the control group.

Table 2: Comparison of some ECG findings between Sicklers and Control N=100

Variables	Sickle cell group(n=50)	Control (n=50)	p-value	Effect size/Odd Ratio
Mean HR (SD)	78.38(12.66)	71.86(12.05)	0.01	0.53
Rhythm				
Sinus	49(98.0%)	50(100.0%)	1.00*	
others	1(2.0%)	0(0.0%)		
RAE				
Present	0(0.0%)	0(0.0%)	1.00*	
Absent	50(100.0%)	50(100.0%)		
LAE			1.00*	
Present	0(0.0%)	0(0.0%)		
Absent	50(100.0%)	50(100.0%)		
QRS Axis				
Normal	50(100.0%)	50(100.0%)	1.00	
Left	0(0.0%)	0(0.0%)		
Right	0(0.0%)	0(0.0%)		
QTc (Male)				
Normal	20(80.0%)	8(33.3%)	<0.001	
Short	3(12.0%)	16(66.7%)		
Prolonged	2(8.0%)	0(0.0%)		
QTc (Female)				
Normal	20(80.0%)	20(80.0%)	0.11	
Short	2(8.0%)	5(20.0%)		
Prolonged	3(12.0%)	0(0.0%)		
QT-Dispersion≥40msec	18(36.0%)	9(18.0%)	0.04	2.6(1.0-6.4)
Present	32(64.0%)	41(72.0%)		
Absent				

**Fischer's Exact Test; HR= Heart Rate; RAE=Right Atrial Enlargement; LAE=Left Atrial Enlargement; LVH=Left Ventricular Hypertrophy; SL-Criteria=Sokolo-lyon Criteria; C-Criteria=Cornell Criteria; A-Criteria=Araoye Criteria; RVH=Right Ventricular Hypertrophy; BVH=Biventricular Hypertrophy.*

Table 3 shows a comparison of QRS voltages between the HbSS group and HbAA. Twenty one (42%) of the sicklers had LVH by Sokolo-lyon criteria, whereas only four (8%) of control group had LVH by the same criteria. This difference was statistically significant (p=<0.001) with LVH by Sokolo-lyon eleven times more likely to occur in the sickle cell group than in the controls. Amongst the males, two of the participants in the sickle cell group had LVH by Cornell voltage criteria, while no participant in the control group had same. This however was not statistically significant (p=0.49). Two female participants in the sickle cell group had LVH by Cornell voltage criteria while no female participant in the control group had same. Thirteen (52%), male participants in the sickle cell group had LVH by Araoye Criteria, while only three (12.5%) male participants in the control group had LVH with the criteria. This difference was statistically significant (P=0.005), with male sickle cell participants seven times more likely to have LVH by Araoye criteria than their HbAA counterparts. Four (16.0%) of the female participants in the sickle cell group had LVH by Araoye criteria while only one (3.8%) female participant in the control group had same. This difference however was not statistically significant (p=0.19). Fifteen (30%) of the participants in the sickle cell group had Right Ventricular Hypertrophy (RVH), while RVH was present in only two (4%) of the participants in the control group. This difference was statistically significant (p=.001). RVH was ten times more likely to occur in the sickle cell group than in the control group. Seven (14%) of the sicklers had Biventricular hypertrophy (BVH), while none of the controls had BVH. This difference in prevalence of BVH was statistically significant (p=0.006).

Table 3: Comparison of Voltage criteria in Study participants

Variables	Sickle cell group (n=50)	Control (n=50)	p-value	Effect size/Odd Ratio
LVH(SL-Criteria)				
Present	21(42.0%)	4(8.0%)	<0.001	11.3(3.1-41.4)
Absent	29(58.0%)	46(92.0%)		
LVH(C-Criteria Male)				
Present				
Absent	2(8.0%)	0(0.0%)	0.49	
	23(92.0%)	24(100.0%)		
LVH(C-Criteria Female)				
Present				
Absent	2(8.0%)	0(0.0%)	0.23	
	23(92.0%)	26(100.0%)		
LVH(A-Criteria Male)				
Present				
Absent	13(52.0%)	3(12.5%)	0.005	7.6(1.8-32.1)
	12(48.0%)	21(87.5%)		
LVH(A-Criteria Female)				
Present				
Absent	4(16.0%)	1(3.8%)	0.19	
	21(84.0%)	25(96.2%)		
RVH				
Present	15(30.0%)	2(4.0%)	0.001	10.3(2.2-47.9)
Absent	35(70.0%)	48(96.0%)		
BVH				
Present	7(14.0%)	0(0.0%)	0.006	
Absent	43(86.0%)	50(100.0%)		

LVH=Left Ventricular Hypertrophy; SL-Criteria=Sokolo-lyon Criteria; C-Criteria=Cornell Criteria; A-Criteria=Araoye Criteria; RVH=Right Ventricular Hypertrophy; BVH=Biventricular Hypertrophy.

Table 4 compares the values of some of the ECG parameters. There was no statistically significant difference in the P wave indices (p=0.51). The mean P wave amplitude in the sickle cell group was 1.24mm while it was 1.31mm in the control group. The mean P wave duration was 0.08s in both groups. The mean P-R Interval, was similar in both groups. The mean PR Interval for the sickle cell group was 0.15, while it was 0.16 for the controls. There was also no statistically significant difference in the mean QRS axis in both groups (p=0.99). The mean QRS axis in the sickle cell group was 43.2 while it was 45.0 in the control group. There was no statistically significant difference in the mean QRS duration of both the HbSS group and controls (p=0.30). The mean QRS duration in both groups was 0.08s. The QTc was significantly longer in the sickle cell group than in the control group. The mean QTc was 0.41s in the sickle cell group while it was 0.38s in the control group (p=<0.001).

Table 4: Comparison of the scores of some ECG parameters between HbSS group and Controls.

N=100

ECG Parameters	Sicklers (n=50)	Controls(n=50)	p-value
P-Wave Amplitude			
Mean(SD)	1.24(0.41)	1.31(0.44)	0.51
95%CI	1.07-1.40	1.13-1.49	
Median	1.00	1.00	
P-Wave Duration			
Mean(SD)	0.08(0.02)	0.08(0.01)	0.72
95%CI	0.06-0.08	0.07-0.08	
Median	0.08	0.08	
P-R Interval			
Mean(SD)	0.15(0.03)	0.16(0.02)	0.13
95%CI	0.15-0.16	0.16-0.17	
Median	0.16	0.16	
QRS Axis			
Mean(SD)	43.20(23.04)	45.00(17.69)	0.99
95%CI	33.68-52.71	35.53-52.47	
Median	60.00	60.00	
QRS-Duration			
Mean(SD)	0.08(0.02)	0.08(0.02)	0.30
95%CI	0.08-0.09	0.07-0.08	
Median	0.08	0.08	
QTc-Interval			
Mean(SD)	0.41(0.03)	0.38(0.16)	<0.001
95%CI	0.04-0.43	0.37-0.39	
Median	0.41	0.38	

**Statistically significant; SD=Standard Deviation; CI=Confidence Interval.*

DISCUSSION

The study showed that ECG abnormalities are more common in patients with sickle cell anaemia than in those with HBAA. The prevalence of electrocardiographic abnormalities in the sickle cell participants in this study was 70%. This is very similar to findings in other studies. Uzsoy et al reported a prevalence of 69.5%.[21] while Dosunmu et al reported a prevalence of 73.1%.[8] In a study by Holloman et al, 72% of the sickle cell participants had ECG abnormalities.[7] These values are similar to the finding in this study. Oguanobi et al, however found a higher prevalence of 96.7%.[22] This could be because they considered a wider range of ECG variables not included in this study, such as non-specific ST segment elevation, T wave inversion in right precordial leads, P wave dispersion and QRS dispersion.[22] In this study, Male sickle cell anemia had a much higher prevalence of ECG abnormalities than females, which tallies with the finding of Dosunmu et al[8] and Holloman et al[7] who also reported a much higher prevalence of ECG abnormalities amongst males. A possible reason for this, could be the observed lower endothelial nitric oxide bioavailability and nitric oxide responsiveness in male sicklers compared to their female counterparts as reported by Gladwin et al.[23] Endothelial nitric oxide, is known to maintain vascular homeostasis, including maintenance of vasodilator tone, reduction in vascular inflammation and injury, hence reduced endothelial NO is a proven cardiovascular risk factor.[24] Another reason why male HbSS patients may have a higher prevalence of ECG abnormalities, could be the documented higher levels of foetal haemoglobin (HbF) in females than in males, with some studies demonstrating that fetal hemoglobin production is controlled by a gene located in the X chromosome. [25,26] HbF does not deoxygenate and polymerize ("sickle") easily hence, HbSS patients with high HbF concentrations have less severe clinical manifestations of SCD.[27] Infact, increasing HbF concentrations with Hydroxyurea is a major therapeutic modality in management of patients with sickle cell anaemia.[28–30]

The HbSS patients had a statistically significant higher mean heart rate than the controls, which is in agreement with several other studies which show that HbSS participants have higher resting heart rates than age and sex matched HbAA controls.[22,31–33] An increase in cardiac output and heart rate is one of the physiologic adjustments to anaemia which is necessary to compensate for the reduced oxygen content of

arterial blood.[34,35] Wolney et al, reported that Sickle cell patients have cardiovascular autonomic dysfunction, impaired baroreceptor reflex sensitivity and impaired heart rate modulation and these may explain the increased heart rate.[36] However, Dosunmu et al reported similar heart rates between the sickle cell group and controls in their study.[8] This may be because they recruited sickle cell patients, who were stable over the prior 3 months as against 4 weeks in this study,[8] hence their participants may have been relatively more healthy.

The most common ECG abnormality in this study was LVH which is also the most common finding in other similar studies. The prevalence of LVH in this study was 42%, which agrees with Dosumnu et al who reported a prevalence of 43%[8]. This is however lower than 75% reported by Oguanobi et al at Enugu[22], but higher than 22% reported by Holloman et al in California U.S.A[7]. Holloman et al used S in V1, plus R in V5 or V6 > 35 mm for patients aged 26 years or older, and > 53 mm for those aged 18 to 25 years.[7] This higher value may account for the lower prevalence of LVH in their study. It is not surprising that LVH is the most common abnormality detected in this study. Sickle cell anaemia has been associated with increased LV mass and cardiomegaly due to chronic volume overload.[4,37] The hemodynamic consequence of chronic anaemia is a hyperdynamic circulation with chronic volume overload resulting in ventricular dilatation and cardiomegaly.[38,39]

Right Ventricular Hypertrophy (RVH) was the next most common abnormality in this study. The prevalence of RVH amongst the cases in this study was 30%, which corroborates the finding of Dosunmu et al, who reported an RVH prevalence of 28% amongst HbSS patients.[8] Oguanobi et al however, reported a lower RVH prevalence of 13.3%.[22] This may be because Oguanobi used a more strict criteria which involved, dominant or tall R waves or Rs pattern in leads aVR, V1 and V2 with deep S wave in leads I, aVL, V5, V6.[22]

The prevalence of biventricular hypertrophy in this study was 14% while none of the controls had BVH. This difference was statistically significant (p=<0.001). This finding is similar to the report by Oguanobi et al who found a BVH prevalence of 11.7%.[22] The increased prevalence of BVH amongst HbSS patients may be a consequence of the chronic hyperdynamic circulation from chronic anaemia. Dosunmu et al found a relatively higher BVH prevalence of 30.3% in their cases.[8] The reason for this is disparity in BVH finding needs further evaluation.

This study found a statistically longer mean QTc amongst the sickle cell participants compared to the controls. This is in agreement with what has been reported by Oguanobi et al,[22] Adebayo et al,[31] Holloman et al,[7] Odia et al,[5] Akgul et al.[40] However, this contrasts with the findings of Dosunmu et al.[8] The explanation could be that Dosumnu et al may have recruited healthier participants since they excluded patients that have had crises within the prior 3 months as against 4 weeks in this study and in other studies. A possible reason why sickle cell anaemia patients may have prolonged QTc is due to the fact that they have myocardial microvascular ischaemia, as has been reported by Desai et al, who proved this with perfusion stress tests conducted in sickle cell patients in Chicago.[41] Prolonged QTc is a marker of repolarization abnormality and a risk for polymorphic ventricular arrhythmia.[42]

This study showed that HbSS participants were significantly more likely to have increased QT dispersion than controls. This is in agreement with the finding of Oguanobi et al.[22] Akgul et al at Turkey, also reported increased QTd amongst HbSS patients in their study.[40] Increased QTd signify regional inhomogeneity and variability in myocardial repolarization.[43] Garadah et al in Bahrain, reported positive correlation between the serum ferritin(a measure of body Iron store) and QT dispersion in adult sickle cell ,/atients.[44] They postulated that iron deposition in the myocardium of sickle cell patients may cause some heterogeneity in myocardial repolarization thereby increasing QT dispersion.[44] Increased QTd poses a risk to arrhythmia development and is a marker of adverse outcome in cardiac diseases.[45]

There was no statistically significant difference in the mean QRS axis and QRS duration between the sickle cell group and controls in this study. This is similar to the findings at Ife, in which all the cases had normal axis, and the QRS duration, between HbSS participants and controls was also similar.[31]

In conclusion, electrocardiographic abnormalities are highly prevalent (70.0%) in adult HbSS patients attending Haematology clinic at Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi in south-east Nigeria. Left ventricular hypertrophy is the most common ECG abnormality seen. Males are much more likely to have an ECG abnormality. Electrocardiographic study should be incorporated into routine diagnostic work up of all adult sickle cell anaemia patients.

Competing Interests

Authors have declared that no competing interest exist

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